

REMARKS

This Amendment and Remarks are filed in response to the Non-Final Office Action dated October 29, 2008. Claims 59-69 and 73-76 are pending and are rejected. Claims 70-72 and 77-86 are withdrawn by Examiner as being directed to non-elected subject matter.

Rejections under 35 USC 112, First Paragraph

Claim 73 and 74 are rejected under 35 U.S.C. 112, first paragraph, as containing a subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Examiner argues that Claims 73 and 74 recite the term " α -tocopherol polyethylene glycol succinate." However, applicant has not conveyed possession of the invention with reasonable clarity to one skilled in the art of the common critical pharmaceutical/chemical feature of the genus of antioxidants that would reasonably provide predictable operability of the invention.

To satisfy the written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date, that applicant was in possession of the claimed invention. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the criticality of selecting a particular antioxidant species, especially an undisclosed antioxidant species, in order to predictably practice the invention as claimed. The term "antioxidant", given its broadest reasonable possible interpretation, encompasses a diverse group of compounds which do not share common chemical or pharmaceutical features. In this case, the

specification fails to provide literal disclosure for the term "α-tocopherol polyethylene glycol succinate", as well as fail to provide adequate written description to reasonably show that said "α-tocopherol polyethylene glycol succinate" is representative of the claimed genus antioxidants as a whole with respect, for example, pharmaceutical/chemical characteristics. Thus, the term "α-tocopherol polyethylene glycol succinate" is found to constitute new matter because an artisan skilled in the art at the time the invention was made would not have been able to reasonable predict the operability of the invention in view of the antioxidant species α-tocopherol polyethylene glycol succinate based on the instant written description which fails to show that said species is representative of the genus of antioxidants as a whole.

Applicants disagree, however, in the interest of advancing the prosecution, Applicants amended claims 73 and 74 by cancelling the "α-tocopherol polyethylene glycol succinate" term and selecting another antioxidant, specifically BHA (butylated hydroxyanisole), disclosed on page 32, line 27.

Rejection is overcome and should be withdrawn.

Rejections under 35 USC 112, Second Paragraph

Claim 62 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 69 recites "[t]he polymer film of claim 66 comprising about 14.9%, by weight, polyethylene oxide, about 59.4% of hydroxypropyl methylcellulose, ... ," which renders the claimed subject matter indefinite because claims 59, 60, and 66, from which claim 69 directly/indirectly depend, fail to provide adequate antecedent basis

for a polymer film comprising two polymer substrates (i.e. polyethylene oxide and hydroxypropyl methylcellulose) because said claims are all directed to a polymer film comprising "a polymer substrate" selected from a Markush group. To the extent that "a" implies a single polymer substrate, the recitation of two polymer substrates in instant claim 69 renders the claimed subject matter indefinite.

Applicants disagree. Claim 59 clearly indicate that any two substrate polymers may be present by the language "alone or in admixture". However, to advance a prosecution, Applicants amended claim 69 to be directed to the admixture of the two substrates.

Rejections is overcome and should be withdrawn.

Rejection under 35 USC § 103

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elsohly et al (US Patent Application Pub. No. 2006/0257463 A1).

This rejection is being made under 103(a) because the teachings of the cited reference do not reasonably envisage the instant relative claimed amounts of the specific ingredients in a transmucosal formulation for vaginal application.

Examiner argues that Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A 1) disclose transmucosal device film or films (in the case of co-extrusion or layering = film sheet) comprising at least one water-soluble, water-swellable or water-insoluble thermoplastic polymer such as, but not limited to, hydroxypropyl cellulose, polyethylene oxide, ... , and hydroxymethyl cellulose); one or more cannabinoid medicaments (= therapeutic agent); a bioadhesive, such as water-soluble or water swellable polymers derived from acrylic acid or a pharmaceutically acceptable salt thereof, including polyacrylic acid polymers (e.g. carbomers, polycarbophils and/or water-soluble salts of

a cop-polymer of methyl vinyl ether and maleic acid or anhydride); one or more pH adjusting agents to improve stability and solubility (e.g. potassium meta phosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate, ethanolamine, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide); and other additives, including penetration enhancers, and/or hydrophobic polymers, cross-linking agents to, for example reduce matrix erosion time (e.g. an organic acid such as tartaric acid, alpha-hydroxy acid, citric acid, fumaric acid, succinic acid), to render the film useful for transmucosal application (par. 0021-0039).

Examiner further argues that Elsohly et al. teach that the transmucosal preparation may also contain other components that modify the extrusion, molding, or casting characteristics or physical properties of the matrix, including, for example, polyethylene, xylitol, sucrose, surface-active agents, ..., and combinations thereof (para. 0026). Elsohly et al. teach transmucosal preparations may comprise super-disintegrants or absorbents e.g. sodium starch glycolate (Explotab or Primojel), croscarmellose sodium (Ac-Di-Sol), cross-linked PVP (Polyplasdone XL 10), clays, alginates, corn starch, potato starch, pregelatinized starch, modified starch, cellulosic agents, ... , gums, ... , and other disintegrants known to those of ordinary skill in the art (para. 0027); transmucosal preparation may also contain an antioxidant (e.g. sodium metabisulfate, sodium bisulfite, vitamin E and its derivatives), chelating agent (e.g. EDTA, polycarboxylic acids, polyamines, and derivatives thereof), stabilizer, surfactant (e.g. sucrose stearate, vitamin E derivatives, sodium lauryl sulfate, dioctyl sodium sulfosuccinate), preservative (e.g. methyl paraben) , ... , flavor, colorant, fragrance and combinations thereof (par. 0028-0039).

Elsohly et al. teach that transmucosal preparations that provide a controlled release of an agent, wherein said preparation contain a suitable release rate modifier, wherein said suitable release rate modifier include: poly (ethylene oxide) or PEG; hydroxypropyl methylcellulose (HPMC); ... , polycarbophil, carbomer or a polysaccharide (par. 0038). Elsohly et al. teach that preferably said transmucosal formulations comprise a penetration enhancer, which may also be referred to as an absorption enhancer or permeability enhancer, which may include bile salts (e.g. sodium deoxycholate), surfactants (e.g. sodium lauryl sulfate, polysorbate 80, laureth-9, benzalkonium chloride, cetyl chloride, and polyoxyethylene monoalkylethers), benzoid acids (e.g. sodium salicylate, methoxy salicylate), fatty acids (e.g. lauric acid, oleic acid, undecanoic acid and methyl oleate), fatty alcohols (e.g. octanol, nonanol), laurocapram, polyols (e.g. propylene glycol, glycerin), cyclodextrins, sulfoxides (e.g. dimethyl sulfoxide and dodecyl methyl sulfoxide), terpenes (e.g. menthol, thymol, and limonene), urea, chitosan and other natural and synthetic polymers; polyoxyethylene monoalkylethers include Brij® and Myrj® series (par. 0016, 0033).

Examiner argues that Elsohly et al. teach a method for increasing the permeability of a patient's mucosa by including a permeability enhancement agent in the transmucosal formulation, wherein said permeability enhancement agent is PEG 400, and/or other enhancers in which cannabinoids may be solubilized; useful solubilizers which may inherently be penetration or absorption enhancers, include, for example, polyethylene glycol (PEG), propylene glycol, dibutyl subacetate, glycerol, diethyl phthalate (phthalate esters), triacetin, citrate esters-triethyl citrate (TEC), acetyltriethyl citrate (ATEC),

tributyl citrate (TBC), acetyltributyl citrate (ATBC), benzyl benzoate, sorbitol, xylitol, Miglyol (glycerides), bis(2-ethylhexyl) adipate, mineral oil, polyhydric alcohols such as glycerin and sorbitol, glycerol esters such as glycerol, triacetate; fatty acid triglycerides such as NEOBEE* M-5 and mineral oil, vegetable oils such as castor oil, etc., polyoxyethylene sorbitan, fatty acid esters such as TWEENS, polyoxyethylene monoalkyl ethers such as BRIJ and MYRJ series, sucrose monoesters, lanolin esters, lanolin ether, and chitosan and other natural and synthetic polymers (par. 0014-0016). Also included as solubilizers for the cannabinoids are organic solvents, such as ethanol, benzene and the like, which may be utilized in solvent cast techniques (par. 0014).

Examiner continues with his rejections by arguing that Elsohly et al. exemplify transmucosal formulations comprising polyethylene oxide (PEG i.e. applicant's elected polymer species) in amounts ranging from 10%-80.4% (par. 0043-0053, including Examples 2-6, and Tables I and III). Elsohly et al. also exemplify transmucosal formulations comprising PEG (10-13%; i.e. polymer substrate), PEG 400 (8-12%; i.e. absorption enhancer/solubilizer/penetration enhancer), citric acid (0.5%), sodium deoxycholate (5%=permeability enhancer/penetration enhancer), methyl paraben (0.2%), THC (8-16% = therapeutic agent = anti-migraine/non-steroidal anti-inflammatory agent/anti-nausea agent), hydroxypropyl cellulose (55.23-63.23%), polyvinyl pyrrolidone 10%, butylated hydroxyl toluene (0.05%), and carbomer (5%). See page 6, par 0051, Table 1).

According to Examiner, Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A 1) teach methods for preparing transmucosal formulations via, for example, hot-melt extrusion, hot-melt molding,

by admixing or utilizing a solvent cast technique, and wherein an effective amount of a cannabinoid is incorporated into the transmucosal cannabinoid-containing preparation, and wherein said transmucosal formulation include a matrix patch for retaining and dispersing the active ingredients (par. 0015). Elsohly et al. teach formulations comprising a bioadhesive system that is an effective, feasible, and convenient intra-oral

drug delivery system for applying and delivering controlled dosages of cannabinoids through or into the oral cavity, which may also be extended to controlled drug delivery in gynecological (vaginal), nasal, sinus, and ophthalmic applications (para. 0019).

Examiner further argues that Elsohly et al. teach single and multi-layered laminated (= sheet) film matrix containing cannabinoids, wherein said matrix can be cut or formed into almost unlimited shapes and sizes, depending on the application and dosage intended (par. 0020). In addition, Elsohly et al. teach that cannabinoids (i.e. non-steroidal anti-inflammatory agents) have various medicinal uses, including treatment of nausea (= anti-nausea agent), pain, migraines (i.e. anti-migraine agent), and rheumatic (i.e. anti-inflammatory effect) and osteo-arthritis (i.e. anti-inflammatory effect), muscle dysfunction associated with multiple sclerosis (par. 0006) and that Elsohly et al. also exemplify transmucosal formulations comprising vitamin E TPGS (= α -tocopherol polyethylene glycol succinate; see par. 0048, Examples 5 and 6).

Examiner makes this rejection under 103(a) because, he admits, **one of skill in the art would not immediately envisage the combination of components as claimed** (Emph. added).

Regardless of the above admission that is contradictory, Examiner

still continues with his rejections because, he argues, it would have been obvious to a person of skill in the art at the time the invention was made to prepare a transmucosal preparation comprising a polymer substrate (e.g. PEG), an anti-migraine agent/anti-nausea agent/non-steroidal anti-inflammatory agent (e.g. THC), a penetration enhancer (e.g. PEG 400), a plasticizer (e.g. propylene glycol), a surfactant (e.g. sodium lauryl sulfate), wherein said transmucosal formulation is in the form of a polymer film sheet for topical application of said anti-migraine agent/anti-nausea agent/non-steroidal anti-inflammatory agent (i.e. THC) to the vaginal epithelium to control pain as taught by Elsohly et al. One would have been motivated to prepare a transmucosal preparation to control pain because Elsohly et al. suggest that transmucosal preparation comprising THC may be useful for treating various conditions, including migraine and arthritis. One would have expected to successfully create said transmucosal formulation because Elsohly et al. teach transmucosal formulations for gynecological/vaginal application.

Examiner further noted that the term "non-steroidal anti-inflammatory agent" given its broadest reasonable possible interpretation is construed to encompass all non-steroidal drugs to exhibit anti-inflammatory activity, including non-steroidal drugs used for treating arthritis e.g. THC and its derivatives as taught by Elsohly et al. It is noted that the instant claimed polymer substrates (e.g. PEG), penetration enhancers (e.g. dioctyl sodium sulfosuccinate, chitosan), plasticizers (e.g. PEG), and surfactants (e.g. polysorbate 80, and sodium lauryl sulfate) overlap with the teachings of the above cited references. In addition, instant claimed amounts of the therapeutic agent (from about 0.1 to about 2000 mg), polymer substrate

(from about 2% to about 100%), penetration enhancer (from about 0.1 to about 60%), plasticizer (from about 5% to about 25%), and surfactant (from about 0.01% to about 5%), all overlap with the teaching of the above cited art (par. 0043-0053, including Examples 2-6, and Tables I and III).

Examiner concludes that, thus, a person of skill in the art at the time the invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Applicants disagree. Applicants respectfully submit that the instant claims are not obvious from Elsholy reference for following reasons.

Applicants invention and instant claims are directed to a polymer film for topical delivery of therapeutic agents. The film is prepared as a **single or double sided** solid or semi-solid film device, such as a film **strip, pad, pillow, tube, sheet, sphere, ring, sheet**, or as a liquid **preparation that forms a film layer** upon contact with an epithelial tissue or with a surface of non-film device made of different material. The film is prepared from an evaporated solution (Spec. page 23, lines 4-13) consisting essentially of a therapeutic agent, substrate polymer, penetration enhancer, surfactant and plasticizer. In order to prepare the film or film as claimed, all these components must be present in ranges specifically claimed to achieve a topical delivery of a therapeutic agent to a vaginal, nasal, buccal, scrotal or labial epithelium **and through** said epithelium into systemic circulation. **At least 55% of the therapeutic agent is released from said film within two hours** (Spec. page 41, lines 9-15 and Figure 2).

Elsholy discloses transmucosal delivery of cannabinoids with a

release pattern, seen in Elsohly, Figure 2, much slower than the instantly claimed release of ketorolac. In two hours interval, only about 12-20% of the cannabinoids of Elsohly are released compared to about 55% of released ketorolac according to the instant invention. Examiner admits that the pharmaceutical agents are different but assigns no value or importance to their chemical differences despite doing so in case of antioxidants (above). As Examiner argues above with regard to antioxidants, his argument is equally applicable to the differences in the instant case. Knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the criticality of selecting a particular THC of Elsohly as an analgesic or anti-inflammatory species, especially when such use is not disclosed in Elsohly, in order to predictably practice the invention as claimed. The term an "anti-inflammatory agent", or "analgesics" encompasses a large and rather diverse group of compounds which do not share common chemical or pharmaceutical features with cannabinoids.

For Examiner's information, applicants show the chemical formulas of the two representative compounds:

Ketorolac chemical formula is $C_{15}H_{13}NO_3 \cdot C_4H_9NO_3$, namely 1H-pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (\pm)-compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) (pharmacoepia).

Cannabinoids have a general formula $C_{21}H_{30}O_2$, namely tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (Merck index).

Applicants submit that the cannabinoids are chemically different compounds than anti-inflammatory compound ketorolac and other claimed therapeutic agents.

The complex chemistry of the claimed therapeutic agents require much more sophisticated formulation of agents than the one disclosed

by Elsohly in order to achieve a film for transmucosal delivery of these compounds having properties, as claimed. In the instant invention, when the formulation and selection of appropriate ratios for each individual therapeutic compound within the claimed ratios that depends on the chemistry of the therapeutic compound is determined, the preparation of the film is very simple and does not require any heat extrusion, molding or drug reservoirs.

When a proper formulation, in a solution, for each individual compound is prepared, the film is formed very simply and practically by spreading or spraying the formulation on the glass, paper or another polymer and allowing it to dry. No heat molding or heat extrusion or solvent casting are necessary. After drying, the film is peeled from the glass or another support and is ready for use as a film device for transmucosal drug delivery.

On the other hand, cannabinoids are very unstable compounds [0050] having a low bioavailability, as disclosed in Elsohly [0010], and consequently, the Elsohly transmucosal preparation requires a solubilization or dispersion of a cannabinoid (0015) into the transmucosal cannabinoid-containing preparation that is prepared by hot-melt extrusion, hot-melt molding, admixing or utilizing a solvent cast technique. The preparation may be a patch or reservoir. The matrix is formed of many matrix formers including polyoxyethylene oxide, hydroxypropyl methylcellulose, gums, agars, etc, and may further contain other components. All exemplarized Elsohly's preparations are prepared by hot-melt extrusion or molding [0042], [0047]. As to the Elsohly's drug release, because of the sensitivity in administering these habit forming compounds, it is important that such release is slow and that the Elsohly film retains a good portion of the cannabinoid for a long time. Thus in the Elsohly's extruded

preparations, close to 99% of the cannabinoids remains in the formulation after 24 hours following the extrusion and close to 96% remain after 12 months following the extrusion [0052]. The Elsohly formulations are therefore very stable and have a very long shelf-life. These properties, of course, affect the drug release from the film and therefore such release is much slower. The release of the cannabinoids from the Elsohly's formulations in first two hours is between approximately 12-20% and does not reach 50% until approximately 22 hours after administration [Figure 2]. Such slow release would not be sufficient and practical for delivery of analgesics or other compounds that need to act quickly and continuously.

Applicants respectfully submit that more than 35% increase of released drug at 2 hours following the film delivery provides distinguishing features making the invention non-obvious.

Applicants respectfully submit that the instant invention and claims are not obvious from the Elsohly reference. The rejection should be withdrawn. It is so respectfully requested.

Examiner further rejects claims 60-69, and 73-76 under 35 U.S.C. 103(a) as being unpatentable over Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A 1), in view of McCoy et al. (US Patent 6,495,120 82), as evidenced by National Library of Medicine - Medical Subject Headings - TPGS alpha-tocopherol polyethylene glycol succinate. 2008, page 1.

Examiner points out that the above discussion of Elsohly et al. is incorporated by reference and admits that Elsohly et al. **do not teach ketorolac.**

Examiner argues that Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A1) teach transmucosal device film or films (in the case of co-extrusion or layering = film sheet) comprising at least one

water-soluble, water-swellaable or water-insoluble thermoplastic polymer such as, but not limited to, hydroxypropyl cellulose, polyethylene oxide, ... , and hydroxymethyl cellulose); one or more canniboid medicaments; a bioadhesive, such as water-soluble or water swellaable polymers derived from acrylic acid or a pharmaceutically acceptable salt thereof, including polyacrylic acid polymers (e.g. carbomers, polycarbophils and/or water-soluble salts of a cop-polymer of methyl vinyl ether and maleic acid or anhydride); one or more pH adjusting agents to improve stability and solubility (e.g. potassium meta phosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate, ethanolamine, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide); and other additives, including penetration enhancers, and/or hydrophobic polymers, cross-linking agents to, for example reduce matrix erosion time (e.g. an organic acid such as tartaric acid, alpha-hydroxy acid, citric acid, fumaric acid, succinic acid), to render the film useful for transmucosal application (para. 0021-0039). Elsohly et al. teach that the transmucosal preparation may also contain other components that modify the extrusion, molding, or casting characteristics or physical properties of the matrix, including, for example, polyethylene, xylitol, sucrose, surface-active agents, ..., and combinations thereof (para. 0026). Elsohly et al. teach transmucosal preparations may comprise super-disintegrants or absorbents e.g. sodium starch glycolate (Explotab or Primojel), croscarmellose sodium (Ac-Di-Sol), cross-linked PVP (Polyplasdone XL 10), clays, alginates, corn starch, potato starch, pregelatinized starch, modified starch, cellulosic agents, ... , gums, ... , and other disintegrants known to those of ordinary skill in the art (para. 0027); transmucosal preparation may also contain an antioxidant (e.g. sodium metabisulfate, sodium bisulfite, vitamins E

and its derivatives), chelating agent (e.g. EDTA, polycarboxylic acids, polyamines, and derivatives thereof), stabilizer, surfactant (e.g. sucrose stearate, vitamin E derivatives, sodium lauryl sulfate, dioctyl sodium sulfosuccinate), preservative (e.g. methyl paraben) , ... , flavor, colorant, fragrance and combinations thereof (paras. 0028-0039). Elsohly et al. teach that transmucosal preparations that provide a controlled release of an agent, wherein said preparation contain a suitable release rate modifier, wherein said suitable release rate modifier include: poly (ethylene oxide) or PEG; hydroxypropyl methylcellulose (HPMC); ... , polycarbophil, carbomer or a polysaccharide (para. 0038). Elsohly et al. teach that preferably said transmucosal formulations comprise a penetration enhancer, which may also be referred to as an absorption enhancer or permeability enhancer, which may include bile salts (e.g. sodium deoxycholate), surfactants (e.g. sodium lauryl sulfate, polysorbate 80, laureth-9, benzalkonium chloride, cetyl chloride, and polyoxyethylene monoalkylethers), benzoid acids (e.g. sodium salicylate, methoxy salicylate), fatty acids (e.g. lauric acid, oleic acid, undecanoic acid and methyl oleate), fatty alcohols (e.g. octanol, nonanol), laurocapram, polyols (e.g. propylene glycol, glycerin), cyclodextrins, sulfoxides (e.g. dimethyl sulfoxide and dodecyl methyl sulfoxide), terpenes (e.g. menthol, thymol, and limonene), urea, chitosan and other natural and synthetic polymers; polyoxyethylene monoalkylethers include Brij® and Myrj® series (par. 0016 , 0033). Elsohly et al. teach a method for increasing the permeability of a patient's mucosa by including a permeability enhancement agent in the transmucosal formulation, wherein said permeability enhancement agent is PEG 400, and/or other enhancers in which cannabinoids may be solubilized; useful solubilizers which may inherently be penetration or absorption enhancers, include, for

example, polyethylene glycol (PEG), propylene glycol, dibutyl subacetate, glycerol, diethyl phthalate (phthalate esters), triacetin, citrate esters-triethyl citrate (TEC), acetyltriethyl citrate (ATEC), tributyl citrate (TBC), acetyltributyl citrate (ATBC), benzyl benzoate, sorbitol, xylitol, Miglyol (glycerides), bis(2-ethylhexyl) adipate, mineral oil, polyhydric alcohols such as glycerin and sorbitol, glycerol esters such as glycerol, triacetate; fatty acid triglycerides such as NEOBEE* M-5 and mineral oil, vegetable oils such as castor oil, etc., polyoxyethylene sorbitan, fatty acid esters such as TWEENS, polyoxyethylene monoalkyl ethers such as BRIJ and MYRJ series, sucrose monoesters, lanolin esters, lanolin ether, and chitosan and other natural and synthetic polymers (par. 0014-0016). Also included as solubilizers for the cannabinoids are organic solvents, such as ethanol, benzene and the like, which may be utilized in solvent cast techniques (par. 0014). Elsohly et al. exemplify transmucosal formulations comprising polyethylene oxide (PEG i.e. applicant's elected polymer species) in amounts ranging from 10%-80.4% (par. 0043-0053, including Examples 2-6, and Tables I and III). Elsohly et al. also exemplify transmucosal formulations comprising PEO (10-13%; i.e. polymer substrate), PEG 400 (8-12%; i.e. absorption enhancer/solubilizer/penetration enhancer), citric acid (0.5%), sodium dexoycholate (5% = permeability enhancer/penetration enhancer), methyl paraben (0.2%), THC (8-16% = therapeutic agent = anti-migraine/non-steroidal anti-inflammatory agent/anti-nausea agent), hydroxypropyl cellulose (55.23-63.23%), polyvinylpyrrolidone 10%, butylated hydroxyl toluene (0.05%), and carbomer (5%). See page 6, para 0051, Table 1). Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A 1) teach methods for preparing transmucosal

formulations via, for example, hot-melt extrusion, hot-melt molding, by admixing or utilizing a solvent cast technique, and wherein an effective amount of a cannabinoid is incorporated into the transmucosal cannabinoid-containing preparation, and wherein said transmucosal formulation include a matrix patch for retaining and dispersing the active ingredients (para. 0015). Elsohly et al. teach formulations comprising a bioadhesive system that is an effective, feasible, and convenient intra-oral drug delivery system for applying and delivering controlled dosages of cannabinoids through or into the oral cavity, which may also be extended to controlled drug delivery in gynecological (vaginal), nasal, sinus, and ophthalmic applications (para. 0019).

Examiner continues to argue that Elsohly et al. teach single and multi-layered laminated (= sheet) film matrix containing cannabinoids, wherein said matrix can be cut or formed into almost unlimited shapes and sizes, depending on the application and dosage intended (para. 0020). In addition, Elsohly et al. teach that cannabinoids (i.e. non-steroidal anti-inflammatory agents) have various medicinal uses, including treatment of nausea (= anti-nausea agent), pain, migraines (i.e. anti-migraine agent), and rheumatic (i.e. anti-inflammatory effect) and osteo-arthritis (i.e. anti-inflammatory effect), muscle dysfunction associated with multiple sclerosis. (para. 0006). Elsohly et al. also exemplify transmucosal formulations comprising vitamin E TPGS (=a-tocopherol polyethylene glycol succinate; see par. 0048, Examples 5 and 6).

However, Examiner admits that Elsohly et al. do not teach NSAIDS (e.g. ketorolac).

According to Examiner, McCoy et al. (US Patent 6,495,120 B2)

McCoy et al. teach formulations that may comprise one or more analgesics as the pharmaceutical agent, including non-narcotic analgesics such as ketorolac and salts thereof (= applicant's elected compound species) for use in controlling pain (col. 3, lines 46-54). McCoy et al. teach exemplary embodiments comprising sodium lauryl sulfate in amounts of 0.9 to 1.2% by weight (col. 4, lines 32-34). McCoy et al. teach stable intra-oral formulations for intra-oral delivery to a patient of a pharmaceutical agent, wherein said formulation comprises a pharmaceutical agent mixed with an orally-acceptable oral absorption enhancer in a orally-acceptable carrier-solvent, wherein the oral-absorption enhancer is adapted to modify the surface membrane such that absorption through the surface membrane is initiated or increased, and wherein the oral-absorption enhancer may comprise hydroxypropyl-beta-cyclodextrin and surfactants, including polysorbate 80, sodium lauryl sulfate, Brig surfactants, Tween and Pluronic surfactants (abstract; col. 4, lines 10-34). McCoy et al. teach formulations, wherein the pharmaceutical agent is present in an amount of about 0.01 to 25% by weight (col. 3, lines 56-59). Also, McCoy et al. teach that the concentration of oral-absorption enhancers (e.g. polysorbate 80, sodium lauryl sulfate) will vary with the particular pharmaceutical agents and/or method of delivery, but typically said oral-absorption enhancers will be present in amounts up to 50% by weight (col. 4, line 27-34).

With respect to the term "a-tocopherol polyethylene glycol succinate" as recited in claims 73 and 74, it is noted by Examiner that the term "Vitamin E TPGS" as taught by Elsohly et al. means α -tocopherol polyethylene glycol succinate as evidenced by the National Library of Medicine - Medical Subject Headings - 2008 (see also

attached Form 892).

Examiner concludes that it would have been obvious to a person of skill in the art to add ketorolac or its salts thereof as taught by McCoy et al. to the transmusocal formulation polymeric film for vaginal application as taught by Elsohly et al. for additive pain/analgesic effect. One would have been motivated to add ketorolac or any of its salts thereof to said transmusocal formulation for additive analgesic/pain effects because Elsohly et al. teach transmusocal formulations comprising analgesic agents (I. e. THC) and ketorolac is also an analgesic agent (Cf. In re Kerkhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980)).

According to Examiner, one would have expected to successfully add ketorolac, and additional optional agents (e. g. BHA or vitamin E TPGS) for delivery of said therapeutic agents to the vaginal epithelium to the transmusocal formulation polymeric film for control pain because Elsohly et al. teach transmusocal formulations for intra-oral and gynecological/vaginal applications and both Elsohly et al. and McCoy et al. teach intra-oral transmusocal drug delivery formulations for enhancing the transmusocal delivery analgesic pharmaceutical agents.

Examiner argues that the instant claimed polymer substrates (e.g. PEO), penetration enhancers (e.g. dioctyl sodium sulfosuccinate, chitosan), plasticizers (e.g. PEG), surfactants (e.g. polysorbate 80, and sodium lauryl sulfate), buffer agents (e.g. sodium bicarbonate) overlap with the teachings of the above cited references. Also, the instant limitation with respect to the thickness of the polymer film of "from 0.5 mm to about 2 mm layer" also overlaps with the teaching of the transmusocal preparations of

approximately 1 mm thickness taught by Elsohly et al. (par. 0047; see instant claim 75). The instant terms "butylated hydroxyanisole (BHA)" (see claims 67 and 69) and α -tocopherol polyethylene glycol succinate (see instant claims 73 and 74) also overlap with the teaching of Elsohly et al. (par. 0037, and 0047-0048).

With respect to the instant claimed combination of PEG and hydroxypropyl methyl cellulose (see instant claim 67), Examiner argues that Elsohly et al. exemplify transmucosal formulations comprising both PEG and hydroxypropyl methyl cellulose (par. 0043, Example 1; see instant claim 67).

In addition, Examiner argues that instant claimed amounts of the therapeutic agent (from about 0.1 to about 2000 mg), polymer substrate (from about 2% to about 100%), penetration enhancer (from about 0.1 to about 60%), plasticizer (from about 5% to about 25%), and surfactant (from about 0.01% to about 5%), all overlap with the teaching of the above cited art (par. 0043-0053, including Examples 2-6, and Tables I and III), and also noted that based on the teaching of Elsohly et al. that solubilizers (e.g. PEG 4000, propylene glycol, Brij, glycerin, triacetin) may function inherently as penetration or absorption enhancers; see para. 0014), it would have been obvious to a person of skill in the art at the time the invention was made to use a solubilizer (e.g. PEG 400) for its dual purpose as an penetration/permeability enhancer and as a solubilizer (i.e. plasticizer) to increase the solubility of the ingredients in the transmucosal formulation. Similarly, it would have been obvious to person of skill in the art at the time the invention was made to use a surfactants such as sodium lauryl sulfate, sodium deoxycholate, polysorbate 80 for their dual effects as surfactants and

penetration/permeability enhancers (see para. 0016).

Examiner further argues that the term "said penetration enhancer ... present in from about 60%, by weight," as recited in claim 62 reads on the term "up to 50% by weight of oral-absorption enhancers" as taught by McCoy et al. (col. 4, line 27-34) because Elsohly et al. teach that penetration enhancers (also referred to as absorption enhancers) may include surfactants such as polysorbate 80, sodium lauryl sulfate (para. 0016). As discussed previously, it is the examiner's position that it would have been within the scope of knowledge and skill of an artisan skilled in the art at the time the invention was made to adjust the relative amounts of the various pharmaceutical ingredients in the transmucosal formulation, including adjusting the amount of the penetration enhancer to an amount of 60% by weight, in order to prepare a stable transmucosal formulation.

Besides, Examiner maintains, McCoy et al. teach that the concentration of oral-absorption enhancers (e.g. polysorbate 80 and sodium lauryl sulfate) will vary with the particular pharmaceutical agents and/or method of delivery (col. 4, line 27-34).

It is the Examiner's position that it would have been within the scope of skill and knowledge of an artisan skilled in the art at the time the invention was made to manipulate the release rate of the transmucosal formulation taught by the prior art to arrive at release rates e.g. a release rate of 50% within 80 minutes = claim 66; and release rates from about 2% to about 7.3%/minute = claims 68 and 70. Further, to the extent that the prior art teaches transmucosal formulations wherein the absorption enhancers (e.g. sodium lauryl sulfate) as well as the amount of said absorption enhancers overlap with the instant permeability enhancers and amount of instant

permeability enhancers in the formulations encompassed by the instant claims, one would reasonably expect the transmucosal formulations taught by the prior art to have similar release rates as the instant claimed formulations (In re Spada).

Examiner concluded that, thus, a person of skill in the art at the time the invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Applicants disagree. Non-obviousness of the instant invention from the Elsohly reference has been discussed above. The relevance of McCoy is questionable as it concerns an intra-oral aerosol or spray delivered by a spray pump or propellant device. Examiner is relying on the components present in formulations of Elsohly and McCoy, including the presence of α -tocopherol polyethylene glycol succinate to make the instant claims obvious without regard of the formulation properties. First, claims 73 and 74 directed to α -tocopherol polyethylene glycol succinate have been amended and this compound is no longer claimed. Second, as shown above, the three inventions are all different and the combination of the two would not derive the third. Ms Coy does not prepare the film at all. The instant film is not the same as the film of Elsohly, it does not have the same properties or release characteristics and no combination of Elsohly with McCoy will result in the film having the instant properties, such as a release rate, as claimed, regardless how combined.

Applicants submit that no single reference cited herein or a combination of two or three references makes the instant invention obvious. Examiner is trying to make his obviousness rejection based on simply reciting the whole reference(s) in 23 pages long Office

Action. However, the number of recited pages does not obviousness make. The Office action is so confusing that no person, skilled in the art or not, could make any sense out of it. Obviousness rejection cannot be based on just reciting all components of the references, twice, in the Office Action.

The instant invention provides and claims a film for transmucosal delivery of drugs that are different and have different physico/chemical properties than the cited prior art Elsohly. The film has different and much faster drug release characteristics than the prior art Elsohly. It is fabricated in a simple and practical way from the solution comprising the drug and other components deposited on a supporting structure, evaporated and removed for use. Neither Elsohly or McCoy prepare the film having the same or similar properties.

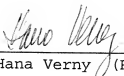
The current claims are not obvious from the cited references or their combination. The rejections should be withdrawn and the newly amended claims passed to issue. It is so respectfully requested.

SUMMARY

In summary, claims 59-69 and 73-76 are amended. Arguments are submitted to overcome rejections under 35 USC 103 and 112. In view of the amendment, it is believed that all rejections are overcome and the claims are in conditions for allowance. Notice of Allowance is respectfully solicited.

Respectfully submitted,
PETERS VERNY, LLP

Dated: March 30, 2009



Hana Verny (Reg. No. 30,518)